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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/525,041	03/14/2000	Daniel R. Soppet	PF178D2	8342

22195 7590 06/30/2003

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EXAMINER
UNGAR, SUSAN NMN

ART UNIT	PAPER NUMBER
1642	29

DATE MAILED: 06/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/525,041	Applicant(s) Soppet et al
	Examiner Ungar	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 11, 2003*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *21-76, 78-101, and 103-126* is/are pending in the application.

4a) Of the above, claim(s) *25, 38-45, 50, 54-71, 90-97, and 116-123* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *21-24, 26-37, 46-49, 51-53, 72-76, 78-89, 98-101, 103-115, and 124-* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The request filed on April 11, 2003 (Paper No. 22) for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/525,041 is acceptable and a CPA has been established. An action on the CPA follows.

2. The Amendment filed April 11, 2003 (Paper No. 22) is acknowledged and has been entered. Previously pending claims 1 and 9-17 have been canceled, claims 99-101 have been amended and new claims 125-126 have been added. Claims 21-24, 26-37, 46-49, 51-63, 72-76, 78-89, 98-102, 103-115, 124-126 are currently being examined.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. The following rejections are maintained:

Claim Rejections - 35 USC § 112

5. Claims 21-24, 26-37, 46-49, 51-63, 72-76, 78-89, 98-102, 103-115 and 124 remain rejected under 35 USC 112, first paragraph and newly added claims 125-126 are rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 20, Section 1, pages 2-5 and in Paper No. 16, Section 4, pages 2-6.

Applicant disagrees with Examiner's finding of lack of enablement based on Examiner's statement that "no one would believe it more likely than not that the presently claimed antibodies are useful for detecting or targeting colon cancer cells" and presents objective evidence, Violette et al "Reg IV, A New Member of the Regenerating Gene Family is Overexpressed in Colorectal Carcinomas", Int. J. Cancer, 2003 103;185-192. Applicant argues that the authors analyzed Reg IV

mRNA expression and then reiterates the conclusion of the authors wherein it is stated that "Our data concerning Reg-IV expression, as assessed by studying the mRNA level, are in accordance with the suggestion of Macadam et al..... that colorectal tumor cells expressing REG proteins have an advantage in terms of survival. Our results suggest that Reg IV-positive cells in colorectal tumors may also have a selective advantage during drug treatment". Applicant argues that the publication demonstrates that in view of mRNA expression data alone, those of ordinary skill in the art would believe it more likely than not that the presently claimed antibodies are useful for detecting or targeting colon cancer cells. The argument has been considered but has not been found persuasive because unlike the polynucleotide encoding SEQ ID NO:2 the REG IV gene is known in the art and although the references specifically states that the REG IV protein has been found in culture medium of a colon cancer line cell, nowhere does the reference suggest that the protein is differentially expressed in primary colon cancer compared to normal colon cells. Examiner takes note of the art recognized artifactural nature of cell lines wherein differences in expression of both mRNA and protein between those found in either primary tumor cells or normal cells are well known in the art, thus data found in cell lines can not be extrapolated to the *in vivo* condition. Further, the enablement of the claimed invention appears to be predicated on the differential expression of SEQ ID NO:2 in tumor cells compared with normal controls. Applicant has presented no evidence that demonstrates that this is in fact the case. Further, the conclusions of Violette et al appear to be based on the suggestions of Macadam et al. Since the Macadam et al paper has not been submitted, Examiner

cannot fully consider the argument since it is not clear whether or not the studies of Macadam et al were drawn to mRNA and/or protein or whether the suggestions found in the reference were based on experimental evidence or were a hypothesis that might be useful for further study, especially in view of the fact that the Macadam et al paper is entitled "Death from early colorectal cancer is predicted by the presence of transcripts of the REG gene family". As previously set forth, based on the mRNA evidence presented it cannot be predicted, and one of ordinary skill would not believe it more likely than not, that the protein encoded by the mRNA is overexpressed in colon cancer because evidence abounds in which protein levels do not correlate with steady-state mRNA levels or alterations in mRNA levels. For instance, Brennan et al (Journal of Autoimmunity, 1989, vol. 2 suppl., pp. 177-186) teach that high levels of the mRNA for TNF alpha were produced in synovial cells, but that levels of the TNF alpha protein were undetectable. Zimmer (Cell Motility and the Cytoskeleton, 1991, vol. 20, pp. 325-337) teaches that there is no correlation between the mRNA level of calcium-modulated protein S100 alpha and the protein level, indicating that S100 protein is post-transcriptionally regulated. Eriksson et al (Diabetologia, 1992, vol. 35, pp. 143-147) teach that no correlation was observed between the level of mRNA transcript from the insulin-responsive glucose transporter gene and the protein encoded thereby. Hell et al (Laboratory Investigation, 1995, Vol. 73, pp. 492-496) teach that cells in all types of Hodgkin's disease exhibited high levels of bcl-2 mRNA, while the expression of the Bcl-2 protein was not homogenous to said cells. Powell et al (Pharmacogenesis, 1998, Vol. 8, pp. 411-421) teach that mRNA levels for cytochrome P450 E1 did not

correlate with the level of corresponding protein, and conclude that the regulation of said protein is highly complex. Carrere et al (Gut, 1999, vol. 44, pp. 55-551) teach an absence of correlation between protein and mRNA levels for the REG protein. Vallejo et al (Biochimie, 2000, vol. 82, pp. 1129-1133) teach that no correlation was found between NRF-2 mRNA and protein levels suggesting post-transcriptional regulation of NRF-2 protein levels. Guo et al (Journal of Pharmacology and Experimental Therapeutics, 2002, vol. 300, pp. 206-212) teach that Oatp2 mRNA levels did not show a correlation with Oatp2 protein levels, suggesting that regulation of the Oatp2 protein occurs at both the transcriptional and post-translational level. These references serve to demonstrate that levels of polynucleotide transcripts cannot be relied upon to anticipate levels of protein expression. Finally, although drawn to changes in mRNA levels for metastasis associated genes in murine tumor cells, the teachings of Jang et al (Clinical and Experimental Metastasis, 1997, vol. 15, pp. 469-483) are relevant to the instant rejection. Jang et al teach that further studies are necessary to determine if changes in protein levels track with changes in mRNA levels for metastasis associated genes in murine tumor cells, thus providing further evidence that one of skill in the art cannot anticipate that the level of a specific mRNA expressed by a cell will be paralleled at the protein level due to complex homeostatic factors controlling translation and post-translational modification. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one to use the claimed invention as contemplated. For

the above reasons, it appears that undue experimentation would be required to practice the claimed invention. Applicants arguments have been considered but have not been found persuasive and the rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 101

6. 35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

7. Claims 21-24, 26-37, 46-49, 51-63, 72-76, 78-89, 98-102, 103-115, 124-126 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility, a substantial utility or a well established utility.

The disclosed utilities for the antibody that binds SEQ ID NO:2 include diagnosis of colon cancer (p. 14, para 2), targeting of cancer cells (p. 17, para 1) *in vivo* imaging (p. 17, para 2, p. 37, para 4), destroying cancer cells *in vivo* (p. 37, para 3). These utilities are based on the utility of the encoded SEQ ID NO:2 whose disclosed utilities include its use for treatment of colon cancer, for screening for compounds which interact with the polypeptide (para bridging pages 4-5), for scientific research, (p. 5), screening for therapeutics to inhibit the action of the polypeptide (p. 26) its use for diagnosing colon cancer by determination of altered levels of the polypeptide wherein level of the polypeptide is determined with an

antibody (p. 14, para 2), screening for receptors, agonists and antagonists (para bridging pages 27 and 28)

However, neither the specification nor any art of record teaches what the encoded SEQ ID NO:2 is, what it does do, do not teach a relationship to any specific diseases or establish any involvement in the etiology of any specific diseases, thus the encoded SEQ ID NO:2 does not have a well established utility. The asserted utilities for the encoded protein such as for screening for compounds which interact with the polypeptide, screening for receptors, agonists and antagonists apply to many unrelated polypeptide structures sequences. Therefore the asserted utilities are not considered "specific" utilities, i.e. they are not specific to the encoded polypeptide. Additional disclosed utilities for the encoded polypeptide include its use for screening for therapeutics to inhibit the action of the polypeptide (p. 26) its use for diagnosing colon cancer by determination of altered levels of the polypeptide wherein level of the polypeptide is determined with an antibody.

The asserted utilities of the encoded protein drawn to diagnosis, treatment, screening for therapeutics appears to be based on the finding that while the colon specific gene is found in all cells of the body, their transcription to mRNA, cDNA and expression products is primarily limited to the colon in non-diseased individuals (p. 11). The specification further teaches that the colon specific gene is overexpressed in colon cancer (p. 33, lines 7-8). However, although it has been demonstrated that the encoded polypeptide is expressed *in vivo*, it is unknown whether or not the encoded polypeptide is differentially expressed in colon cancer

as compared with normal cells. Additional experimentation would be required in order to determine whether or not the encoded polypeptide is differentially expressed and the encoded polypeptide does not have substantial utility. Since the encoded polypeptide does not have substantial utility, the claimed antibody also does not have substantial utility because additional experimentation would be required in order to determine whether or not the claimed antibody would be effective at imaging cancer, targeting cancer, treating cancer based on the differential expression of the encoded polypeptide. In particular, as disclosed above, evidence abounds in which protein levels do not correlate with steady-state mRNA levels or alterations in mRNA levels. For instance, Brennan et al (Journal of Autoimmunity, 1989, vol. 2 suppl., pp. 177-186) teach that high levels of the mRNA for TNF alpha were produced in synovial cells, but that levels of the TNF alpha protein were undetectable. Zimmer (Cell Motility and the Cytoskeleton, 1991, vol. 20, pp. 325-337) teaches that there is no correlation between the mRNA level of calcium-modulated protein S100 alpha and the protein level, indicating that S100 protein is post-transcriptionally regulated. Eriksson et al (Diabetologia, 1992, vol. 35, pp. 143-147) teach that no correlation was observed between the level of mRNA transcript from the insulin-responsive glucose transporter gene and the protein encoded thereby. Hell et al (Laboratory Investigation, 1995, Vol. 73, pp. 492-496) teach that cells in all types of Hodgkin's disease exhibited high levels of bcl-2 mRNA, while the expression of the Bcl-2 protein was not homogenous to said cells. Powell et al (Pharmacogenesis, 1998, Vol. 8, pp. 411-421) teach that mRNA levels for cytochrome P450 E1 did not correlate with the level of corresponding

protein, and conclude that the regulation of said protein is highly complex. Carrere et al (Gut, 1999, vol. 44, pp. 55-551) teach an absence of correlation between protein and mRNA levels for the Reg protein. Vallejo et al (Biochimie, 2000, vol. 82, pp. 1129-1133) teach that no correlation was found between NRF-2 mRNA and protein levels suggesting post-transcriptional regulation of NRF-2 protein levels. Guo et al (Journal of Pharmacology and Experimental Therapeutics, 2002, vol. 300, pp. 206-212) teach that Oatp2 mRNA levels did not show a correlation with Oatp2 protein levels, suggesting that regulation of the Oatp2 protein occurs at both the transcriptional and post-translational level. These references serve to demonstrate that levels of polynucleotide transcripts cannot be relied upon to anticipate levels of protein expression. Further, Jang et al (Clinical and Experimental Metastasis, 1997, vol. 15, pp. 469-483) teach that further studies are necessary to determine if changes in protein levels track with changes in mRNA levels for metastasis associated genes in murine tumor cells, thus providing further evidence that one of skill in the art cannot anticipate that the level of a specific mRNA expressed by a cell will be paralleled at the protein level due to complex homeostatic factors controlling translation and post-translational modification. Thus additional experimentation is required to determine whether or not the encoded protein is differentially expressed in colon cancer as compared to normal cancer cells Additional experimentation must be carried out before the claimed antibody can be used as contemplated. Thus, neither the claimed antibody nor the expressed polypeptide have substantial utility. Although the claimed antibody may be used for isolation of SEQ ID NO:2, this is not a specific utility because all antibodies may be used to isolate the molecule to

which they bind. Thus, this utility applies to all antibodies and it is not specific to the claimed antibody. Given the above, the specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the claimed antibody. Because the claimed invention is not supported by a well established utility, a specific utility, a substantial utility for the reasons set forth, credibility of any utility cannot be assessed. The rejection can be obviated by submission of objective evidence demonstrating that SEQ ID NO:2 is differentially expressed in primary colon cancer compared with normal colon cells.

Claim Rejections - 35 USC § 112

8. Claims 21-24, 26-37, 46-49, 51-63, 72-76, 78-89, 98-102, 103-115, 124-126 are rejected under 35 U.S.C. 112, first paragraph.

Specifically, since the claimed invention is not supported by a well established utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention. The rejection can be obviated by submission of objective evidence demonstrating that SEQ ID NO:2 is differentially expressed in primary colon cancer compared with normal colon cells.

9. Claims 125-126 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of an antibody that binds to the lectin domain of SEQ ID NO:2/the lectin domain of a polypeptide encoded by the cDNA in ATCC Deposit Number 97129 has no clear support in the specification and the claims as originally filed. Applicant points to page 6, first paragraph for support of the newly amended claims.

However, a review of page 6 first paragraph reveals support for a polynucleotide encoding the colon specific gene which contains an open reading frame encoding a protein of 158 amino acid residues which has a 36% structural homology to a galactose specific lectin from a diamondback rattlesnake with a 54% similarity over a 125 amino acid stretch and 30% identity and 52% similarity to a human pancreatic stone protein precursor. The suggested support is not persuasive because the support is not drawn to a lectin domain within SEQ ID NO. 2. A review of the specification did not reveal that SEQ ID NO:2 had a lectin domain, no nexus between SEQ ID NO:2 and a lectin domain was taught or suggested. There is no teaching that SEQ ID NO:2 comprises a consensus lectin domain. There is no guidance in the specification regarding an antibody that binds to the lectin domain of SEQ ID NO:2 and no suggestion that the antibody claimed binds to a lectin domain. The subject matter claimed in claims 125-126 broadens the scope of the invention as originally disclosed in the specification.

10. All other rejections and objections recited in Paper No. 16 are hereby withdrawn.

11. No claims allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
June 22, 2003